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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,429	02/22/2002	William A. Haseltine	PF106P3D1	9565

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,429	HASELTINE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005 and 22 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-60* is/are pending in the application.

4a) Of the above claim(s) *5,6,8,17-21,35,36 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-13,16,22-34,37-54 and 56-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040223*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply; U.S.P.T.O. Partial copy of search report "us-10-079-429a-4.rup" (pages 1 and 2); and copy of a memorandum by A. Patterson dated January 14, 2003 (pp. 1-3).

DETAILED ACTION

1. The election with traverse filed August 9, 2005, is acknowledged and has been entered. Applicant has elected the invention of Group V, claims 22-34, 37-54, and 56-60, insofar as the claims are drawn to an antibody that binds a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4 and a cell or hybridoma that produces said antibody.

2. The amendment filed August 9, 2005, is acknowledged and has been entered. Claim 14 has been canceled. Claims 1, 3, 13, and 18 have been amended. Claims 22-60 have been added.

3. Claims 1-13 and 15-60 are pending in the application. Claims 5, 6, 8, 15, 17-21, 35, 36, and 55 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 9, 2005.

4. Claims 1-4, 7, 9-13, 16, 22-34, 37-54, and 56-60 are currently under prosecution.

Election/Restrictions

5. Applicant's traversal of the restriction and election requirement set forth in the preceding Office action mailed June 10, 2005, is acknowledged.

At page 12 of the paper filed August 9, 2005, Applicant has requested clarification that the inventions of Group V are antibodies that bind hMLH2 proteins, as represented, for example, by the protein of SEQ ID NO: 4 and the protein encoded by the cDNA contained in ATCC Deposit No. 75651. In response, as indicated at page 3 of the Office action mailed June 10, 2005, the inventions of Group V are antibodies that bind a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4 and a

cell or hybridoma that produces said antibody, as recited in claims 14, 22-34, 37-54, and 56-60. Group V does not include claims directed to antibodies that bind a polypeptide having the deduced amino acid sequence of SEQ ID NO: 2, or a cell or hybridoma that produces such an antibody.

At page 13, Applicant has requested rejoinder of claims directed to the inventions of Groups I, III, V, VII, and IX. Applicant's arguments have been found persuasive in part. Accordingly, the claims of Groups I, III, and V have been rejoined; therefore, claims 1-4, 7, 9-13, 16, 22-34, 37-54, and 56-60 are currently under prosecution to the extent that those claims are directed to a nucleic acid molecule, a vector comprising said nucleic acid molecule, a host cell comprising said vector, a method for producing a polypeptide comprising culturing said host cell, a method for producing said host cell, wherein said nucleic acid molecule encodes a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, a polypeptide comprising the deduced amino acid sequence of SEQ ID NO: 4, an antibody that binds said polypeptide, and a cell or hybridoma that produces said antibody.

Claims directed to the inventions of VII and IX have not been rejoined because contrary to Applicant's arguments the search required to examine claims directed to either of these inventions is not the same, nor is coextensive with the necessary search of the above noted subject matter of claims 1-4, 7, 9-13, 16, 22-34, 37-54, and 56-60. As such, consideration of claims directed to the inventions of VII and IX would be unduly burdensome.

Since the inventions of Groups I, III, and V and either of the inventions of Groups VII and IX are patentably distinct from the other for the reasons set forth in the preceding Office action, and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

Nevertheless, as Applicant elected product claims, it is again noted where Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise**

include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Accordingly, Applicant's remarks at page 14 of the amendment filed August 9, 2005, have been addressed.

6. Claims 6 and 15 were erroneously included in Group I, as these claims are directed to a polynucleotide encoding a polypeptide encoded by the cDNA of ATCC Deposit No. 75649, which the specification discloses in the polypeptide designated hMLH1 (i.e., the polypeptide of SEQ ID NO: 2); see, e.g., paragraphs [0021], [0028], and Figure 1. As such, claims 6 and 15 should have been included in another group, which is not identified in the restriction and election requirement, with claims drawn to a

nucleic acid molecule, a vector comprising said nucleic acid molecule, a host cell comprising said vector, a method for producing a polypeptide comprising culturing said host cell, and a method for producing said host cell, wherein said nucleic acid molecule encodes a polypeptide having the deduced amino acid sequence of SEQ ID NO: 2. For this reason, as indicated above, claims 6 and 15 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

7. The information disclosure filed February 23, 2004, has been considered. An initialed copy is enclosed.

Oath/Declaration

8. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration by Nikolas Papadopoulos. See 37 CFR 1.52(c).

Inventorship

9. In view of the papers filed March 10, 2003, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of the following inventors: Bert Vogelstein, Kenneth W. Kinzler, Nicholas C. Nicolaides, and Nickolas Papadopoulos.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

10. Regarding the statement under 37 C.F.R. § 1.48(a)(2) by Nickolas Papadopoulos filed March 10, 2003, it is noted that the inventor's last name had been misspelled as "Papadopolous". Correction of this misspelling has been made by the Examiner.

Priority

11. Applicant's claim under 35 USC § 120 for benefit of the earlier filing dates of U.S. Patent Application Serial No. 08/210,143, filed March 16, 1994, and U.S. Patent Application Serial No. 08/187,757, filed January 27, 1994, is acknowledged.

However, claims 1-4, 9-13, 16, 22-34, 37-54, and 56-60 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of these priority documents because neither document describes SEQ ID NO: 4. Accordingly, the earliest effective filing date of the claims is deemed the filing date of U.S. Patent Application Serial No. 08/294,312, namely August 23, 1994.

Furthermore, to receive benefit of the earlier filing date under 35 USC §120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Because claims 1, 2, 7, 9-13, 16, 31-33, 51-53, and 56-60 are rejected herein under 35 U.S.C. § 112, first paragraph, as failing to satisfy either the written description or enablement provisions, or both, these claims are deemed to have the filing date of the instant application, namely February 22, 2002.

Drawings

12. The drawings set forth as Figure 1, 2, 3, and 4 are objected to because the figures depict polynucleotide and/or amino acid sequences, which are not identified by sequence identification numbers, either in the figures or in the brief descriptions of figures. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief descriptions of the figures at paragraphs [0021]-[0024] of the specification to include references to the necessary sequence identification numbers.

Specification

13. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the polynucleotide and/or amino acid sequences depicted in Figures 1, 2, 3, and 4 are not identified by sequence identification numbers, either in the figure or in the brief descriptions of figures.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences

appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

14. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark is Isee™ (paragraph [0135]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

15. The specification is objected to because the brief description of figures 1-4 at paragraphs [0021]-[0024] does not properly indicate that each includes multiple sheets consecutively labeled in alphabetical order. Appropriate correction is required. For example, the brief description of Figure 1 at paragraph [0021] should be amended to read, "Figure 1 (A-F) illustrates [...]".

Claim Objections

16. Claims 1, 2, and 9-13 are objected to as being drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

17. Claim 1 is objected to because the claim twice recites the same limitation under (a) and (c) that the claimed polynucleotide comprises "a polynucleotide encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO:4 or a fragment of said polypeptide". Appropriate correction is required.

18. Claim 13 is objected to because the claim twice recites the same limitation under (a) and (c) that the claimed polynucleotide comprises "a polypeptide having the deduced amino acid sequence of SEQ ID NO:4 and fragments thereof". Appropriate correction is required.

19. Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 16 is drawn to the polynucleotide of claim 1 comprising "a polynucleotide sequence of at least 15 and no more than 30 consecutive bases of the polynucleotide sequence of ATCC Deposit No. 75651". The polynucleotide of claim 1 is, in the alternative, a polynucleotide comprising a polynucleotide sequence encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, or a polynucleotide encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651. The specification discloses the amino acid sequence encoded by the cDNA contained in the deposited material to which the claim refers has been deduced to be the amino acid sequence of SEQ ID NO: 4; see, e.g., Figure 2. As such, claim 16 does not properly limit the subject matter of claim 1, since "a polynucleotide sequence of at least 15 and no more than 30 consecutive bases of the polynucleotide sequence of ATCC Deposit No. 75651" cannot be a polynucleotide

comprising "a polynucleotide sequence encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4", nor can it be a polynucleotide comprising "a polynucleotide encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651". Accordingly, claim 16 may further limit claim 1 only insofar as it is directed to a polynucleotide comprising a polynucleotide sequence encoding a fragment of the polypeptide having the deduced amino acid sequence of SEQ ID NO: 4. A proper dependent claim must further limit the subject matter of a preceding claim in its entirety, and not just part thereof.

This issue may be remedied, for example, by adding a claim directed to the polynucleotide of claim 1, wherein said polynucleotide encodes a fragment of said polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, and then amending claim 16 to depend from this added claim.

Claim Rejections - 35 USC § 101

20. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

21. Claim 13 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, as evidenced by Nicolaides et al. (*Nature*. 1994 Sep 1; **371** (6492): 75-80) (of record) and the attached copy of part of U.S.P.T.O. search report "us-10-079-429a-4.rup".

As evidenced by Result 1 beginning at page 1 of the attached copy of part of U.S.P.T.O. search report "us-10-079-429a-4.rup", which was generated by searching the database UNIPROT using SEQ ID NO: 4 as a query, SEQ ID NO: 4 is 100% identical to the amino acid sequence in the database having the accession number P54277. According to the annotations of this amino acid sequence, it is identical to the amino acid sequence encoded by the polynucleotide sequence in the database GenBank™, which has the accession number U13695. Nicolaides et al. teaches the

amino acid sequence of the protein that is encoded by the polynucleotide sequence of GenBank™ Accession Number U13695 (page 76, Figure 1).

Claim 13 is drawn to a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4 and fragments thereof, or a polypeptide encoded by the cDNA of ATCC Deposit No. 75651, which the specification teaches is a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4.

As evidenced by Nicolaides et al., the polypeptide having the amino acid sequence set forth as SEQ ID NO: 4 (i.e., hPMS1, which is designated in this application "hMLH2") is naturally occurring in humans; see entire document (e.g., page 76, Figure 1).

The polypeptide of claim 13 is not necessarily isolated, nor is it purified, for example, such that it is distinguishable from the naturally occurring human protein designated "hMLH2/hPMS1", which has an amino acid sequence identical to that set forth in this application as SEQ ID NO: 4.

Accordingly, claim 13 is drawn to non-statutory subject matter, since, as written, it does not sufficiently distinguish over products that exist naturally. Moreover, the claim does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980).

This issue may be remedied by amending claim 13 to recite, for example, "isolated" before "polypeptide" in the first line. See M.P.E.P. § 2105.

22. Claims 9 and 10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 9 is drawn to a vector containing a polynucleotide encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, or encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651, which the specification teaches has been deduced to be the amino acid sequence set forth in this application as SEQ ID NO: 4.

None of the subject matter of claims 9 or 10 is necessarily isolated. Accordingly, claim 9 encompasses the vector, which is comprised within a host cell, following transformation or transfection of a cell by the vector, and claim 10 encompasses the host cell, which is comprised with an animal.

At paragraph [0066] the specification describes the host cell as a higher eukaryotic cell, such as a mammalian cell; and given the disclosure at paragraphs [0057]-[0102], for example, which teaches "gene therapy", it is apparent the cell to which claim 10 refers may be a human cell comprised within a living patient. Furthermore, given this disclosure at paragraphs [0057]-[0102], and the accompanying descriptions of the vector, it is apparent that the vector to which claim 9 refers may be a vector (e.g., a recombinant retroviral vector), which has been used as a means to deliver the "gene therapy" to cells comprised within the human body.

Therefore, claims 9 and 10 are broadly, but reasonably interpreted to encompass vectors comprised within human cells, and such human cells, respectively, which are comprised within in the body of patients treated using gene therapy. Inasmuch, the claims are broadly but reasonably interpreted to encompass human beings.

MPEP § 2105 [R-1] states:

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.

This issue can be remedied by amending claims 9 and 10 to recite, "isolated", before "vector" and "host cell", respectively. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

23. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

24. Claims 11, 12, 16, 26, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites, "said DNA". Claim 11 depends from claims 10/9/1. The polynucleotide, as recited in claim 1, to which the preceding claims refer is not necessarily DNA, as evidenced, for example, by claim 2, which further limits the polynucleotide of claim 1 to DNA. Accordingly, the recitation of "said DNA" in claim 11 finds no antecedent basis. Therefore, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 11 is indefinite because the claim is directed to a method for producing a polypeptide; yet, the claim merely recites the process comprises expressing from the host cell of claim 10 the polypeptide encoded by said DNA. There is no process step that clearly relates back to the purpose or objective of the claimed invention; consequently, the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of the claim. Thus, in the absence of a correlative step positively relating the whole of the process to its intended use, as recited in the preamble, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

This issue may be remedied by amending claim 11 to recite, for example, the additional phrase, "whereby said polypeptide is produced".

Claim 12 is similarly indefinite because it also does not recite a correlative step positively relating the whole of the process to its intended use, as recited in the preamble.

This issue may be remedied by amending claim 12 to recite, for example, the additional phrase, "whereby said cells are produced".

Furthermore, claim 12 is indefinite because, although drawn to a method for producing cells capable of expressing a polypeptide, as it only requires genetically

engineering cells with the vector of claim 9, it is unclear whether its intended use is to produce the polypeptide encoded by the vector of claim 9, or some other polypeptide. Then, for this reason also, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

This latter issue may be remedied by amending claim 12 to recite, for example, "for producing cells capable of expressing a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4 comprising genetically engineering cells with the vector of claim 9, wherein said polynucleotide of claim 1 encodes said polypeptide".

Claim 16 is indefinite because the claim recites, "the polynucleotide sequence of ATCC Deposit No. 75651". Claim 1 is directed to a polynucleotide encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651. It is unclear whether it is to the polynucleotide sequence of the cDNA contained in the deposited material, as opposed to any other polynucleotide sequence of ATCC Deposit No. 75651 claim 16 refers. Thus, claim 1 does not provide proper and sufficient antecedent basis for this recitation in claim 16. Therefore, claim 16 fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

This issue may be remedied by amending claim 16 to recite, for example, "the polynucleotide sequence of the cDNA contained in ATCC Deposit No. 75651".

Claim 26 is indefinite because it is drawn to the antibody or fragment thereof of claim 23 that binds protein (b). Claim 23 is drawn to the antibody or fragment thereof of claim 22 that binds protein (a). As recited in claim 22, "protein (a)" is a protein consisting of amino acids 1 to 932 of SEQ ID NO: 4. As also recited in claim 22, "protein (b)" is a protein consisting of a portion of SEQ ID NO: 4, which comprises at least 30 contiguous amino acids of SEQ ID NO: 4. A protein that necessarily consists of the entirety of SEQ ID NO: 4 (i.e., amino acids 1 to 932 of that sequence), such as the

protein to which claim 23 is directed, cannot also *consist of* a mere portion of that sequence, as would be required by claim 26. Accordingly, claim 26 fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 47 is indefinite because it is drawn to the antibody or fragment thereof of claim 44 that binds protein (b). Claim 44 is drawn to the antibody or fragment thereof of claim 43 that binds protein (a). As recited in claim 43, "protein (a)" is a protein consisting of amino acids 1 to 932 of SEQ ID NO: 4. As also recited in claim 43, "protein (b)" is a protein consisting of a portion of SEQ ID NO: 4, which comprises at least 30 contiguous amino acids of SEQ ID NO: 4. A protein that necessarily consists of the entirety of SEQ ID NO: 4 (i.e., amino acids 1 to 932 of that sequence), such as the protein to which claim 44 is directed, cannot also *consist of* a mere portion of that sequence, as would be required by claim 47. Accordingly, claim 47 fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

25. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. Claims 31-33, 51-53, and 56-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 31 and 51 are drawn to "labeled" antibodies or fragments thereof. Although the specification, including the claims, as originally filed, describes labeled nucleic acids (e.g., paragraph [0042]; paragraph [0134]) and labeled polypeptides (e.g., paragraph [0137]), it does not appear "labeled" antibodies. Accordingly, it appears that the addition of claims 31 and 51 has introduced new matter, thereby violating the written description provision set forth under 35 U.S.C. § 112, first paragraph.

Claims 32, 52, and 60 are drawn to antibodies or fragments thereof that specifically bind to the protein "in a Western Blot". At paragraph [0094] the specification discloses, "*the detection of a specific DNA sequence* may be achieved by methods such as hybridization, RNase protection, chemical cleavage, Western Blot analysis [...]" (italicized for added emphasis), but this disclosure hardly describes a subgenus of antibodies that bind specifically to a protein, such as the polypeptide of SEQ ID NO: 4, upon an analysis of a blot using such antibodies. Thus, the specification, including the claims, as originally filed, does not appear to describe such a subgenus of antibodies and fragments thereof, which bind the protein "in a Western Blot". Accordingly, it appears that the addition of claims 32, 52, and 60 has introduced new matter, thereby violating the written description provision set forth under 35 U.S.C. § 112, first paragraph.

Claims 33 and 53 are drawn to a genus of isolated cells that produce the antibody or fragment thereof of claims 23 and 44, respectively. At paragraph [0115] the specification describes the preparation of monoclonal antibodies of the invention may achieved by any technique that provides antibodies produced by continuous cell line cultures, such as the hybridoma technique disclosed by Kohler et al. (1975), the trioma technique, the human B-cell hybridoma technique described by Kozbor et al. (1983), and the EBV-hybridoma technique described by Cole et al. (1985). Then, at paragraph [0116] the specification describes techniques for the production of single chain antibodies, such as those disclosed by U.S. Patent. No. 4,946,778, and, here, it also describes transgenic mice for the production of humanized antibodies. Thus, the specification adequately provides written support for the hybridomas, for example, to

which claims 34 and 54 are directed, but none of these disclosures, or any other appear to provide written support for the broad genus of "cells" to which claims 33 and 53 are directed, which are capable of producing the antibody or fragment thereof of claims 23 and 44, respectively. Moreover, the breadth of the written description of the genus of "cells" is simply not reasonably commensurate with the breadth of the claims. Accordingly, it appears that the addition of claims 33 and 53 has introduced new matter, thereby violating the written description provision set forth under 35 U.S.C. § 112, first paragraph.

Claims 56-60 are directed to antibodies or fragments thereof that specifically bind "an hMLH2 protein expressed in a cell" or "an hMLH2 protein purified from a cell culture". While it is believed that there is at least implied support for the claimed antibody or fragment thereof that binds "an hMLH2 protein purified from a cell culture", the specification, including the claims, as originally filed, does not appear to provide the proper and sufficient written support for the claimed antibody or fragment thereof that binds "an hMLH2 protein expressed in a cell". It is not particularly clear what structural and/or functional features characterize the claimed antibody that binds "an hMLH2 protein expressed in a cell", but if the claimed antibody an intrabody (i.e., an antibody or fragment thereof recombinantly expressed intracellularly in a cell expressing hMLH2), the specification, as filed, hardly provides written support for claims drawn to such an antibody or fragment thereof. Accordingly, it appears that the addition of claims 56-60 has introduced new matter, thereby violating the written description provision set forth under 35 U.S.C. § 112, first paragraph.

At page 10 of the amendment filed February 10, 2004, Applicant has asserted that the added claims add no new matter, as written support is found for the language of the added claims throughout the specification, as originally filed. In particular, Applicant has pointed to paragraphs [0053], [0078], and [0109]-[0112]. Contrary to Applicant's assertions, none of these particular paragraphs appears to provide written support for any of the rejected claims.

Any of the above issues might be remedied if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are

believed to provide the necessary written support for the language of the rejected claims.

27. Claims 1, 2, 7, 9-13, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105).

Furthermore, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Claims 1, 2, and 9-12 are directed to a genus of polynucleotides comprising a polynucleotide encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4 *or a fragment thereof.* Therefore, claims 1, 2, and 9-12 are not solely directed to polynucleotides comprising a polynucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, but rather encompass any polynucleotide comprising a polynucleotide sequence encoding a mere portion of such a polypeptide (e.g., an amino acid, or a fragment of the amino acid sequence of SEQ ID NO: 4). Accordingly, the claims are directed to a genus of polynucleotides that vary substantially in both structure and function, which might not encode a protein, or might encode a protein that is both structurally and functionally dissimilar from the polypeptide of SEQ ID NO: 4. Although the specification describes a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, and also describes two other proteins, which are disclosed as functionally related, it does not describe how the polypeptide of SEQ ID NO: 4, or any other polypeptide, is regarded as representative of the genus of polypeptide encoded by the claimed polynucleotides. Moreover, there is no description of any particularly identifying (i.e., substantial) structural feature that is shared by the members of the genus of proteins encoded by the claimed genus of polynucleotides, which correlates with any particularly identifying functional feature, which is common among at least a substantial number of its members.

Claim 13 is drawn to a genus of structurally and functionally disparate polypeptides comprising mere "fragments" of a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4. Again, there is no description of any particularly identifying (i.e., substantial) structural feature that is shared by the members of the genus of polypeptides, which correlates with any particularly identifying functional feature, which is common among at least a substantial number of its members.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Without adequate description of the claimed genus of variant species of polynucleotides, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of its members, and therefore the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Claim 7, which depends from claim 1, recites the limitation, "wherein said polynucleotide encodes a polypeptide encoded by the cDNA of ATCC Deposit No.

75651". Accordingly, the claim should be broadly but reasonably interpreted to encompass any member of a genus of polynucleotides according to claim 1, which encodes any member of a genus of polypeptides encoded by the cDNA of ATCC Deposit No. 75651. The specification, however, describes the cDNA of ATCC Deposit No. 75651 *as encoding only one polypeptide*, namely the polypeptide of the amino acid sequence set forth as SEQ ID NO: 4. Therefore, despite the fact that claim 7 is an original claim, in the absence of a description of the genus of polypeptides that are encoded by the cDNA, the skilled artisan could not immediately envision, recognize, or distinguish its members, and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Although claim 16 is indefinite for the reason explained in the rejection of the claim under 35 U.S.C. § 112, second paragraph, in the interest of advancing prosecution, it is herein interpreted to read on a polynucleotide comprising at least 15 and no more than 30 consecutive nucleotides of the polynucleotide sequence of ATCC Deposit No. 75651. It is unclear what biologic material (e.g., a cell transfected with a vector comprising the cDNA encoding hMLH2, or a plasmid containing the cDNA, or perhaps the isolated cDNA) constitutes that deposit, but if it such a cell or such a plasmid, the deposit contains polynucleotide sequences, in addition to the polynucleotide sequence of the cDNA, that have not been described to any extent. Accordingly, the polynucleotide sequence of ATCC Deposit No. 75651, *per se*, has not been described; rather it appears that, at best, the polynucleotide sequence of the cDNA contained in the deposited material is disclosed, presuming that that polynucleotide sequence is depicted in Figure 2. Even so, claim 16 is not limited to a polynucleotide consisting of the polynucleotide sequence depicted in Figure 2, nor is it limited to a polynucleotide consisting of a fragment of this polynucleotide sequence. Instead, claim 16 is drawn to a genus of structurally and functionally different polynucleotides sharing only the common structural feature of having a polynucleotide sequence comprising a mere fragment of the polynucleotide sequence of ATCC Deposit No. 75651, whatever that may be. Thus, claim 16 is drawn to members of a genus of

nucleic acid molecules, which, even given benefit of the disclosure, could not be immediately envisioned, recognized or distinguished by the skilled artisan. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail below in the rejection of claims as lacking an enabling disclosure, there is in fact such unpredictability associated with the practice of the relevant art.

28. Claims 1, 2, 7, 9-13, 16, and 56-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, an isolated vector containing said polynucleotide, an isolated host cell genetically engineered with said vector, a process for producing said polypeptide comprising culturing said host cell that expresses said polynucleotide, a process for producing said isolated host cells, an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, a polynucleotide consisting of a fragment of said polynucleotide, which comprises at least 15, but not more than 30 contiguous nucleotides of said polynucleotide sequence, an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4, a polypeptide consisting of a fragment of said amino acid sequence, and an isolated antibody or fragment thereof that binds specifically to said polypeptide or to a

polypeptide consisting of a fragment of said amino acid sequence, **does not reasonably provide enablement for making and using** an isolated polynucleotide *comprising* a polynucleotide sequence encoding *a fragment* of a polypeptide having the amino acid sequence of SEQ ID NO: 4, an isolated polynucleotide of claim 1 encoding *any* polypeptide encoded by cDNA of ATCC Deposit No. 75651, a polypeptide comprising a fragment of a polypeptide having the amino acid sequence of SEQ ID NO: 4, a polynucleotide comprising a polynucleotide sequence of at least 15, but no more than 30 consecutive nucleotides of the polynucleotide sequence of ATCC Deposit No. 76561, or an isolated antibody or fragment thereof that specifically binds an hMLH2 protein expressed in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to

practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above "written description" rejection of claims 1, 2, 7, 9-12, and 16, these claims are directed to a genus of polynucleotides that vary substantially in both structure and function, which might encode a protein, but which encode a protein having markedly different structures and functions from those features of the polypeptide of SEQ ID NO: 4. As also explained in the above rejection, claim 13 is drawn to a genus of structurally and functionally disparate polypeptides comprising "fragments" of a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4. The skilled artisan cannot make what has not been adequately described, but even so, because the claims are directed to a genus of functionally variant polynucleotides, which encode functionally disparate polypeptides, or to a genus of functionally disparate polypeptides, the skilled artisan would not know how to use the claimed invention and would be left to elaborate a use for most of the polynucleotides or polypeptides encompassed by the claims. Such a need to elaborate uses for the claimed invention would constitute a need to perform undue and/or unreasonable experimentation.

This position is further supported by reference cited in the paragraphs below, which establish the state of the art, the level of skill in the art, and the unpredictability associated with the practice of the art.

Though the claims are *not* limited to polynucleotides encoding polypeptides that are necessarily either structurally or functionally related, Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar

overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science.* 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the possible nucleic acids and the proteins encoded thereby, which fall within the scope of the claims, the skilled artisan could not recognize which of these would function similarly to a protein comprising SEQ ID NO: 4, and which would not.

Furthermore, although the polypeptide of SEQ ID NO: 4 is disclosed as having a role in DNA repair, the specification does not describe which amino acid residues of the polypeptide of SEQ ID NO: 4 are essential to that activity or which must be retained to preserve that activity. Moreover, the specification does not teach which amino acids in the sequence of the polypeptide can be replaced, and by which other amino acids, without a loss of that activity. Again, as evidenced by the teachings of Skolnick et al. and Bowie, for example, the skilled artisan cannot accurately and reliably predict whether a given homologue of a particular protein known to have a certain activity will also have that activity. In addition, the skilled artisan cannot reliably and accurately predict the functional and structural consequences of amino acid differences; but the more structurally disparate a given protein, the less likely the protein will share the function of structurally related proteins having known functions. Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and

biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

Consistently, Luque et al. (*Biochemistry.* 2002 Nov 19; **41** (46): 13663-13671) reported that substitution of a single highly conserved amino acid in baculovirus *Orgyia psuedotsugata* Op-IAP and *Drosophila* DIAP1 abolishes the function of the proteins, as defined by their ability to bind apoptosis stimulators, including *Drosophila* Hid and mammalian Smac/DIABLO; see entire document (e.g., the abstract). Although the amino acid replaced is highly conserved and might therefore have been reasonably expected to be essential to the function of the protein, because the inhibitor of apoptosis proteins have more than one specific activity, some residues, which although conserved, may not be important to specific activities, whereas others are. The skilled artisan cannot predict which conserved amino acid residues are critical to which specific activities of such multifunctional proteins. For example, Vucic et al. (*J. Biol. Chem.* 1998 Dec 18; **273** (51): 33915-33921) performed a mutational analysis of baculovirus inhibitor of apoptosis Op-IAP and found that, although most of the conserved amino acid residues in the BIR2 motif were revealed to be essential to the protein's ability to inhibit apoptosis, most of these conserved residues were not required for binding to Hid; see entire document (e.g., the abstract). A region at the carboxy-proximal end of BIR2 was essential for binding to Hid (apoptosis). Vucic et al. disclose that these results show that binding to Hid is necessary but not sufficient to block Hid-induced apoptosis (abstract). Thus, while it is possible to determine which amino acids residues are conserved in various different family members, it is not possible to predict which of these conserved residues are critical to the various different functions of a multifunctional protein.

Echoing this fact, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid change may be sufficient to cause the acquisition of a new ligand binding specificity as well as to suppress recognition of a previous ligand, extending observations by others who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA.* 2004 Jun 22; **101** (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be 34% ± 6% (abstract); that is, 34% of random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein

(i.e., the so-called "*x* factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, Lazar et al., for example, shows that even a single, conservative amino acid change can cause substantial changes in the activity of a protein, so it is evident that the skilled artisan cannot predict the functional consequences of amino acid substitutions and must determine those consequences empirically; and since Guo et al. shows that amino acid substitutions are remarkably likely to cause inactivation of the protein, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given variant of a protein can be used in the same manner in which the protein having a known function is used.

With regard to claims 56-60, as explained in the above "new matter" rejection of those claims under 35 U.S.C. § 112, first paragraph, it is not particularly clear what structural and/or functional features characterize the claimed antibody that binds "an hMLH2 protein expressed in a cell". Nevertheless, the claims are reasonably interpreted to read on an intrabody (i.e., an antibody or fragment thereof recombinantly expressed intracellularly in a cell expressing hMLH2). The specification, however, does not teach one to make or use such an antibody or fragment thereof.

In addition, as explained in the above rejection of claims 9 and 10 under 35 U.S.C. § 101, the claims are broadly but reasonably interpreted to read on vectors and host cells comprised within the human body following treatment of the human using the vector. With further regard to claims 11 and 12, given the disclosure at paragraphs [0057]-[0102], it is apparent that the objective of "gene therapy" is to produce cells comprised within a living patient that are capable of expressing, or capable of producing the polypeptide that is encoded by a vector, such as the vector of claim 9 to which both claims 11 and 12 refer. In other words, these claims read on treatment processes termed in the art as "gene therapy".

The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the

specification does not remedy and would preclude the skilled artisan from making and using the claimed invention without undue and/or unreasonable experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum by Dr. Amy Patterson dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention without undue and/or unreasonable experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

There is a suggestion that the invention might be used to treat hereditary nonpolyposis colon cancer (HNPCC), or other hereditary diseases and cancers. Ferrari et al. (*Clin. Exp. Immunol.* 2003; **132**: 1-8) addresses the immunological hurdles to lung cancer gene therapy, which, even more recently, continue to hinder the successful clinical application of such treatments and yet which have not been resolved by the instant disclosure; see entire document (e.g., the abstract). Ferrari et al. teaches that although gene transfer to the lung is feasible, gene expression from both viral and non-viral vectors has been inefficient and inflammatory, antibody, and T cell responses limit transgene expression duration and readministration (abstract), just as earlier published references also indicate. So, despite advancements in the art of gene therapy, the same limitations that hindered its successful therapeutic application in past years continue to hamper its clinical use today. It is believed that although Ferrari et al. does not particularly address the limitations of using gene therapy to treat, for example, HNPCC, the reference is no less pertinent to a determination the sufficiency of the instant disclosure to enable the use of the claimed invention, since regardless of the type of cancer or hereditary disease objectively treated, such the problems and limitations described are for the most part common. As such problems and limitations have yet to be remedied, it is apparent that the disclosure cannot be regarded as sufficiently enabling the use of the claimed invention as of the filing date sought by Applicant.

In addition, with particular regard to claims 7 and 16, which are directed to the biological material of ATCC Deposit No. 75651, it is unclear if biological material having the exact structural and chemical identity of deposited material to which the claims refer

is known and publicly available, or can be reproducibly produced or isolated without undue experimentation. Claim 7, as explained above, is not limited to a polynucleotide encoding the polypeptide of SEQ ID NO: 4, but rather encompasses a genus of polynucleotides comprising a polynucleotide sequence encoding *a polypeptide* encoded by the cDNA of ATCC Deposit No. 75651, which the specification describes only as encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4. The amino acid sequences of the other polypeptides encoded by the cDNA are not known. Claim 16, as also explained above, is drawn to a polynucleotide comprising a fragment of the polynucleotide of ATCC Deposit No. 75651, which is not known to be the polynucleotide sequence of the cDNA contained in this deposited material. Even if it were, claim 16 is drawn to a *particular species* of polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4 (i.e., that which is contained in the deposited material), as opposed to a genus of polynucleotides encoding such a polypeptide. Therefore, in the case of either claim, it is unclear if biological material having the exact structural and chemical identity of deposited material to which the claims refer is known and publicly available, or can be reproducibly produced or isolated without undue experimentation.

Although at paragraph [0046] the specification discloses the deposited material is provided merely as a convenience, it is not clear that the sequence of the cDNA contained in the deposited material, which encodes a polypeptide having a deduced amino acid of SEQ ID NO: 4, is identical to the polynucleotide sequence depicted in Figure 2. Therefore, without access to the deposited biological material to which the claims refer, or, absent assurance that the sequence of the cDNA is identical to the polynucleotide sequence depicted in Figure 2, without the ability to reproduce this material, it would not be possible to practice the claimed invention.

The specification describes the deposit having the ATCC Accession No. 75651 as having been deposited January 25, 1994; see, e.g., paragraph [0027]. Furthermore, at paragraph [0046], the specification discloses the following:

> The deposit(s) referred to herein will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for purposes of Patent Procedure. These deposits are provided merely as convenience to

> those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112. The sequence of the polynucleotides contained in the deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are incorporated herein by reference and are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

These disclosures, however, are not sufficient to satisfy the enablement requirements set forth under 35 U.S.C. § 112, first paragraph, nor do they provide sufficient assurance that all the conditions of M.P.E.P. § 608.01(p)(c) have been met. This is particularly true, given the express disclosure in the specification that "[a] license may be required to make, use or sell the deposited materials, and no such license is hereby granted" (paragraph [0046]). See 37 C.F.R. §§ 1.801-1.809.

As the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

30. Claims 1, 2, 7, 9-13, 16, 32, 33, 52, 53, and 56-60 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/20678 A1.

WO 95/20678 A1 (Haseltine et al.) teaches a biologic deposit having the ATCC Accession No. 75651; see entire document (e.g., page 7). Haseltine et al. teaches the deposited material contains a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4 (e.g., page 7, Figure 2; SEQ ID NO: 4). Haseltine et al. teaches the disclosed polypeptide is a human protein designated "hMLH2" (e.g., page 8). Haseltine et al. teaches the polynucleotide encoding this protein may be DNA (e.g., page 9). Haseltine et al. teaches vectors and host cells comprising the polynucleotide encoding this protein, which are cultured to produce the protein (e.g., page 13). Haseltine et al. teaches the host cells are genetically engineered with the vector (e.g., page 13). Haseltine et al. teaches polynucleotides consisting of fragments of the polynucleotide sequence encoding the protein, which are 15-30 nucleotides in length (e.g., page 22). Haseltine et al. teaches antibodies and fragments thereof (e.g., monoclonal antibodies; Fab) that bind the protein and cells (e.g., hybridomas) that produce such proteins (e.g., pages 28 and 29).

Although Haseltine et al. does not expressly teach the antibody that binds the protein is capable of doing so in a Western blot, the monoclonal antibody, for example, which is disclosed is reasonably expected to bind specifically to the protein under the

conditions utilized in Western blot analysis, as with no known exceptions, all such monoclonal antibodies are believed useful in Western blot analysis of the protein to which they specifically bind.

31. Claims 1-4, 7, 9-13, 16, 22-30, 32, 33, 34, 37-50, 52, 53, 54, and 56-60 are rejected under 35 U.S.C. 102(e) as being anticipated by either U.S. Patent No. 6,416,984 B1 or U.S. Patent No. 6,380,369 B1.

Although the applied references have different inventive entities, they have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, they constitute prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the references was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Both U.S. Patent No. 6,416,984 B1 and U.S. Patent No. 6,380,369 B1 teach a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 4; see entire documents (e.g., Figure 2). In addition, both teach a biologic deposit having the ATCC Accession No. 75651 (e.g., column 4). Both teach the deposited material contains a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 4 (e.g., columns 3 and 4; Figure 2; SEQ ID NO: 4). Both teach the disclosed polypeptide is a human protein designated "hMLH2" (e.g., columns 4 and 5). Both teach the polynucleotide encoding this protein may be DNA (e.g., column 4 ('369), or column 5 ('984)). Both teach vectors and host cells comprising the polynucleotide encoding this protein, which are cultured to produce the protein (e.g., columns 8-11). Both teach the host cells are genetically engineered with the vector (e.g., column 7 ('369), or column 8 ('984)). Both teach polynucleotides consisting of fragments of the polynucleotide sequence encoding the protein, which are 15-30 nucleotides in length (e.g., column 11 ('369), column 12 ('984)). Both teach antibodies and fragments thereof (e.g., monoclonal antibodies; Fab) that bind the protein and cells

(e.g., hybridomas) that produce such proteins (e.g., column 14 ('369), column 14 ('984)).

Although neither reference expressly teaches the antibody that binds the protein is capable of doing so in a Western blot, the monoclonal antibody, for example, which is disclosed is reasonably expected to bind specifically to the protein under the conditions utilized in Western blot analysis, as with no known exceptions, all such monoclonal antibodies are believed useful in Western blot analysis of the protein to which they specifically bind.

For clarity, although the applied references commonly claim benefit of the same priority documents, namely U.S. Patent Application Serial No. 08/210,143, filed March 16, 1994, nor U.S. Patent Application Serial No. 08/187,757, filed January 27, 1994, as explained above under "***Priority***", claims 1-4, 9-13, 16, 22-34, 37-54, and 56-60 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of these priority documents because *neither of these earlier filed patents describes SEQ ID NO: 4.* Accordingly, the earliest effective filing date of the claims 1-4, 9-13, 16, 22-34, 37-54, and 56-60 is deemed the filing date of U.S. Patent Application Serial No. 08/294,312 (i.e., August 23, 1994). Then, as further explained under "***Priority***", because claims 1, 2, 7, 9-13, 16, 31-33, 51-53, and 56-60 are rejected herein under 35 U.S.C. § 112, first paragraph, as failing to satisfy either the written description or enablement provisions, or both, these claims are deemed to have the filing date of the instant application, namely February 22, 2002. While the priority documents (i.e., U.S. Patent Application Serial Nos. 08/210,143 and 08/187,757) do not describe SEQ ID NO: 4, absent a showing otherwise, they nevertheless are believed to provide an enabling disclosure of the subject matter encompassed by the instant claims, which is also disclosed by the applied references. For example, although not disclosing the amino acid sequence of SEQ ID NO: 4, the earlier filed applications describe a polypeptide encoded by the cDNA contained in a biologic deposit having the ATCC Accession No. 75651. Absent a showing otherwise, the amino acid sequence encoded by this cDNA is deemed the same as the amino acid sequence of the claimed polypeptide, or the same as the amino acid sequence encoded by the claimed polynucleotide. This position is believed

reasonable because the instant claims are directed to the amino acid sequence of the polypeptide encoded by the cDNA contained in the deposit identified by the same accession number, and the accession number of an ATCC deposit is a unique and unambiguous identifier of the deposited material. Therefore, the applied references are properly deemed prior art under 35 U.S.C. § 102(e) because the priority documents to which they claim benefit provide an enabling disclosure of that anticipatory subject matter, which is therefore described in a patent granted on an application for patent by another filed in the United States before the invention by the Applicant.

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. Claims 31 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/20678 A1 in view of Nakane (*Int. J. Dev. Biol.* 1993 Mar; **37** (1): 85-87).

WO 95/20678 A1 (Haseltine et al.) teaches that which is set forth above in the rejection of claims 1, 2, 7, 9-13, 16, 32, 33, 52, 53, and 56-60 are rejected under 35 U.S.C. 102(b).

However, Haseltine et al. does not teach or suggest the antibody is labeled, so as to permit one to detect the antibody, for example.

Nakane discusses the "peek at the future through histological preparations" (abstract). Nakane teaches antibodies are detectably labeled with, for example, peroxidase, which permits the antibody to be detected (abstract). Nakane teaches such labeled antibodies are useful in histochemistry and immunochemistry (abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time invention was made to have labeled the antibody disclosed by Haseltine et al. One ordinarily skilled in the art at the time invention was made would have been motivated to

have done so because Nakane teaches such a labeled antibody is useful in histochemistry and immunochemistry, as, for example, the antibody could be used to study the expression of the protein to which it binds in tissues.

34. Claims 31 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,416,984 B1 or U.S. Patent No. 6,380,369 B1 in view of Nakane (*Int. J. Dev. Biol.* 1993 Mar; **37** (1): 85-87).

U.S. Patent No. 6,416,984 B1 and U.S. Patent No. 6,380,369 B1 teach that which is set forth above in the rejection of claims 1-4, 7, 9-13, 16, 22-30, 32, 33, 34, 37-50, 52, 53, 54, and 56-60 are rejected under 35 U.S.C. 102(e).

However, neither reference teaches or suggests the antibody is labeled, so as to permit one to detect the antibody, for example.

Nakane discusses the "peek at the future through histological preparations" (abstract). Nakane teaches antibodies are detectably labeled with, for example, peroxidase, which permits the antibody to be detected (abstract). Nakane teaches such labeled antibodies are useful in histochemistry and immunochemistry (abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time invention was made to have labeled the antibody disclosed by either U.S. Patent No. 6,416,984 B1 or U.S. Patent No. 6,380,369 B1. One ordinarily skilled in the art at the time invention was made would have been motivated to have done so because Nakane teaches such a labeled antibody is useful in histochemistry and immunochemistry, as, for example, the antibody could be used to study the expression of the protein to which it binds in tissues.

Double Patenting

35. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

36. Claims 1-4, 7, and 13 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,610,477 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-4 and 7 of the instant application are drawn to a polynucleotide comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651, which the specification teaches has been deduced to be the amino acid sequence of SEQ ID NO: 4; see, e.g., Figure 1. Claim 13 is drawn to a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, or to a polypeptide encoded by the cDNA of ATCC Deposit No. 75651.

Claim 11 of U.S. Patent No. 6,610,477 B1 is drawn to a process comprising assaying a sample derived from a human to determine the presence of a mutation in the

polypeptide sequence of a gene comprising a polynucleotide encoding the same mature polypeptide encoded by the human cDNA ATCC Deposit No. 75651.

Accordingly, Claim 11 of U.S. Patent No. 6,610,477 B1 teaches a polypeptide encoded by a cDNA contained in a biological material deposited under ATCC Deposit No. 75651.

The deposit number of a biological material uniquely and unambiguously identifies a deposited material.

As such, claim 11 of U.S. Patent No. 6,610,477 B1 teaches a polynucleotide comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. 75651, which has been deduced to be the amino acid sequence of SEQ ID NO: 4; moreover, claim 11 of U.S. Patent No. U.S. Patent No. 6,610,477 B1 teaches a polypeptide having the amino acid sequence of SEQ ID NO: 4.

37. Claims 1-4, 7, 9-12, and 16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,380,369 B1 (of record). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-4 and 7 are drawn to a polynucleotide comprising a polynucleotide sequence encoding a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4, or encoding a polypeptide encoded by the cDNA of ATCC Deposit No. 75651, which the specification discloses is a polypeptide having the deduced amino acid sequence of SEQ ID NO: 4. Claim 9 is drawn to a vector comprising the polynucleotide sequence of claim 1. Claim 10 is drawn to a host cell genetically engineered with the vector of claim 9. Claim 11 is drawn to a method for producing a polypeptide comprising expressing from the host cell of claim 10 the polypeptide encoded by said polynucleotide. Claim 12 is drawn to a process for producing cells capable of expressing a polypeptide comprising genetically engineering cells with the vector of claim 9.

Claims 1-62 of U.S. Patent No. 6,380,369 B1 teach a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, a vector and a host cell comprising such a polynucleotide, and a method for producing said polypeptide comprising culturing the host cell.

The claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application. In particular, although none of claims 1-62 of U.S. Patent No. 6,380,369 B1 expressly teach "genetically engineering" the host cells with the vector comprising the polynucleotide encoding the polypeptide, given the conventionality of such a process at the time the application was filed, such a difference would have been obvious to one of ordinary skill in the art.

38. Claims 1-4, 7, 9-12, and 16 are directed to an invention not patentably distinct from claims 1-62 of commonly assigned U.S. Patent No. 6,380,369 B1. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above rejection of claims 1-4, 7, 9-12, and 16 on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 6,380,369 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

39. Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-48 of U.S. Patent No. 6,416,984 B1 (of record). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claim 13 of the instant application is drawn to a polypeptide comprising the amino acid sequence of SEQ ID NO: 4.

Claims 21-48 of U.S. Patent No. 6,416,984 B1 teach a polypeptide comprising the amino acid sequence of SEQ ID NO: 4.

40. Claim 13 is directed to an invention not patentably distinct from claims 21-48 of commonly assigned U.S. Patent No. 6,416,984 B1. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above rejection of claim 13 on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 6,416,984 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

41. No claim is allowed.

42. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Casciola-Rosen et al. (*Arthritis Rheum.* 2001 Feb; **44** (2): 389-396) teaches naturally occurring autoantibodies that bind hPMS1 (i.e., hMLH2).

43. Applicant is advised that should claim 3 be found allowable, claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

44. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
February 8, 2006

Notice to Comply	Application No.	Applicant(s)	
	10/079,429	HASELTINE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: As noted in the Office action, this application is deficient because the sequences depicted in Figs. 1-4 are not identified; if necessary to correct the deficiency, Applicant must provide substitute copies of the Sequence Listing together with an amendment directing its entry and a statement that both are the same and include no new matter, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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